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Copper-Catalyzed Enantioselective Hetero-Diels–Alder Reaction of Danishefsky's Diene with β,γ-Unsaturated α-Ketoesters

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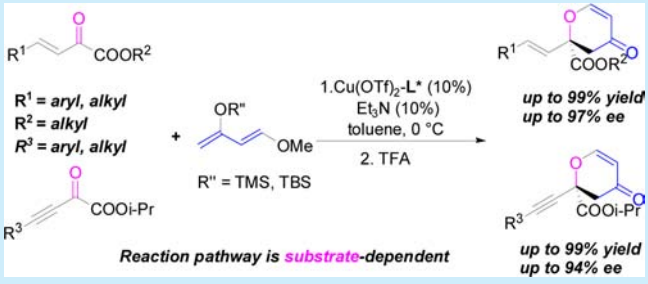
Supporting Information

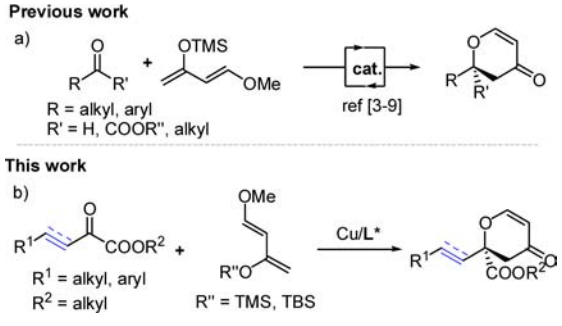
ABSTRACT: A highly enantioselective hetero-Diels–Alder reaction of Danishefsky's diene with β,γ-unsaturated α-ketoesters was developed for the first time by virtue of chiral copper complexes. This protocol provided a facile access to optically active dihydropyranones bearing a quaternary center with high enantioselectivities and good yields. Furthermore, on the basis of the isolated intermediate analysis, the reaction pathway was substrate-dependent.



The hetero-Diels–Alder (HDA) reaction provides a powerful tool to construct aza, oxa-heterocycle molecules in organic synthesis.[1] Since Danishefsky et al. identified the *trans*-1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene)[2] as an active diene, many useful chiral Lewis acid catalysts have been utilized to catalyze the HDA cycloaddition of Danishefsky's diene with aldehydes or ketones.[3] Recently, the List group developed a chiral disulfonimide as an efficient catalyst for the HDA reaction of aldehydes with Danishefsky's diene or substituted dienes, which led to the efficient synthesis of 2,5,6-trisubstituted dihydropyrones.[4] Compared with aldehyde/ketone, the HDA reactions of bicarbonyl dienophiles with Danishefsky's diene are relatively fewer (Scheme 1a).[5]

Jørgensen et al. described the first highly enantioselective HDA reaction of α-ketoesters with Danishefsky's diene,[6] and this type of reaction was further developed by the Loh group.[7] The Ghosh group[5a,c] and the Mikami group[5g] reported the transformation of glyoxylates with Danishefsky's diene catalyzed by Cu-BOX, chiral Ti complexes, respectively. Besides, chiral rare earth organophosphates were demonstrated to be efficient catalysts for the HDA reaction of phenylglyoxylates by Inanaga et al.[8] Recently, the Wolf group reported a multisubstrate one-pot high-throughput screening method for the HDA reaction of glyoxylates with the diene.[9]

Scheme 1. Previous Study and This Work on Hetero-Diels–Alder Reaction



To the best of our knowledge, the Cu-catalyzed asymmetirc HDA reaction between Danishefsky's diene and β,γ-unsaturated α-ketoesters[10] has not been reported so far. Herein, we report the first HDA reaction of Danishefsky's diene with β,γ-unsaturated α-ketoesters to afford chiral dihydropyrones bearing a quaternary center using copper complexes (Scheme 1b). The unsaturated bonds (alkene or alkyne) in the resulting dihydropyranones allow further derivatization. The mechanism study showed that the reaction pathway was substrate-dependent.

First, (*E*)-isopropyl 2-oxo-4-phenylbut-3-enoate **1a** was selected as a model dienophile to conduct the cycloaddition with Danishefsky's diene. Based on our group's efforts on chiral Cu–Schiff base and Cu–prolinol derivative complexes,[11] three catalytic systems were tested to obtain the product **3a** with high enantioselectivity (Table 1). When dinuclear copper complex[11b] (entry 1) and monodentate N-ligand directed zinc complex[11a] (entry 2) were employed as the catalysts, a low yield and poor enantioselectivity were obtained. To our delight, the *ee* value was improved when a chiral copper–prolinol (**L2**) complex was used (entry 3).

Encouraged by these results, the reaction conditions were further optimized (Table 2). First, the equivalent of Danishefsky's diene was varied to enhance the yield (entries 1–5). The use of 2.0 equiv of the diene proved to be the best condition, giving the dihydropyrone **3a** in 77% yield (entry 4).

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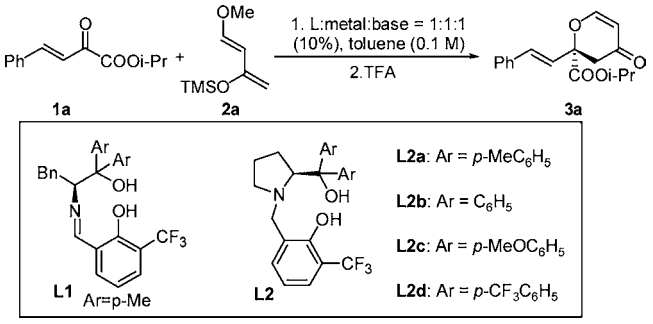
Table 1. Screening of Catalytic Systems[a]



entry	ligand	metal	base	yield[d] (%)	ee[e] (%)
1	L1	$CuBr_2$	piperidine[b]	18	24
2	L1	$Zn(OTf)_2$	piperidine[c]	28	41
3	L2a	$Cu(OTf)_2$	Cs_2CO_3	39	93

[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.11 mmol), **L** (10 mol %), base (10 mol %), and metal salt (10 mol %) in toluene (1.0 mL) at 0 °C. [b]2.0 equiv. [c]3.0 equiv. [d]Isolated yield. [e]Determined by chiral HPLC analysis. Tf = trifluoromethanesulfonyl.

Table 2. Optimization of Reaction of 1a with 2a[a]

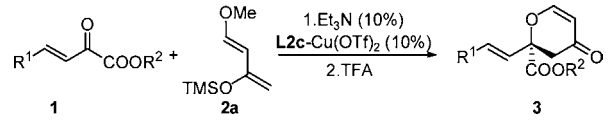
entry	ligand	base	**2a** (equiv)	yield[b] (%)	ee[c] (%)
1	**L2a**	Cs_2CO_3	1.25	54	90
2	**L2a**	Cs_2CO_3	1.50	65	90
3	**L2a**	Cs_2CO_3	1.75	71	89
4	**L2a**	Cs_2CO_3	2.0	77	91
5	**L2a**	Cs_2CO_3	3.0	76	91
6	**L2a**	K_2CO_3	2.0	85	92
7	**L2a**	DBU	2.0	87	93
8	**L2a**	piperidine	2.0	80	94
9	**L2a**	*t*-BuONa	2.0	49	90
10	**L2a**	Et_3N	2.0	84	95
11	**L2b**	Et_3N	2.0	77	95
12	**L2c**	Et_3N	2.0	94	95
13	**L2d**	Et_3N	2.0	77	95

[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (corresponding equivalent), **L2** (10 mol %), base (10 mol %), and $Cu(OTf)_2$ (10 mol %) in toluene (1.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Further screening of the base showed that Et_3N was the best choice for the reaction with respect to the yield and enantioselectivity (entry 10). The electronic property of the aryl moiety of the ligand was examined next (entries 10−13). The electron-donating group on the aryl moiety of **L2** could give a better result than the electron-withdrawing group (entry 12 vs 10−11, 13). When **L2c** was employed as the catalyst, the best result could be obtained, in which dihydropyrone **3a** could be obtained in 94% yield and 95% *ee* (entry 12).

With the optimal conditions in hand, the substrate scope of *β,γ*-unsaturated *α*-ketoesters for the HDA reaction was explored (Table 3). The electronic effect was examined by changing the *para*-substituents of R^1 (entries 2−7). In terms of electron-donating groups, the methyl and methoxyl groups were tolerated well, affording the products **3b** and **3c** with excellent yield and enantioselectivity (entries 2−3). Electron-withdrawing groups, such as fluoro-, bromo-, and chloro-groups, had little influence on the reaction (entries 4−6). The strong electron-withdrawing effect favored the yield but had

Table 3. Scope of *β,γ*-Unsaturated *α*-Ketoesters[a]



entry	R^1	R^2	time (h)	**3**	yield[b] (%)	ee[c] (%)
1	C_6H_5	*i*-Pr	16	**3a**	94	95
2	*p*-MeC_6H_4	*i*-Pr	20	**3b**	90	95
3[d]	*p*-$OMeC_6H_4$	*i*-Pr	24	**3c**	90	97
4	*p*-FC_6H_4	*i*-Pr	20	**3d**	95	96
5	*p*-BrC_6H_4	*i*-Pr	17	**3e**	93	96
6	*p*-ClC_6H_4	*i*-Pr	17	**3f**	95	96
7	*p*-$NO_2C_6H_4$	*i*-Pr	17	**3g**	99	96
8	*m*-ClC_6H_4	*i*-Pr	20	**3h**	99	94
9	*o*-ClC_6H_4	*i*-Pr	17	**3i**	81	97
10	(*E*)-cinnamyl	*i*-Pr	17	**3j**	96	93
11	2-naphthyl	*i*-Pr	16	**3k**	94	96
12[d]	2-thienyl	*i*-Pr	16	**3l**	97	96
13	*n*-pentyl	*i*-Pr	20	**3m**	84	96
14	cyclohexyl	*i*-Pr	17	**3n**	96	97
15	C_6H_5	Me	20	**3o**	97	95
16	C_6H_5	Et	20	**3p**	97	96
17	C_6H_5	*t*-Bu	24	**3q**	85	93
18	C_6H_5	Bn	20	**3r**	97	96

[a]Unless otherwise noted, all reactions were performed with **1** (0.2 mmol), **2a** (0.4 mmol), **L2c** (10 mol %), Et_3N (10 mol %), and $Cu(OTf)_2$ (10 mol %) in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]MTBE as the solvent. MTBE = Methyl *tert*-butyl ether.

little influence on the enantioselectivity (entry 7). Substitution at other positions on the phenyl group was also compatible with this reaction condition (entries 8−9). Unsaturated (*E*)-cinnamyl groups and ring-fused groups were also successfully employed, giving products **3j** and **3k** in excellent yields and enantioselectivities (entries 10−11). When a heterocyclic group, such as a 2-thienyl group, was employed, an excellent yield and enantioselectivity were obtained (entry 12). More importantly, excellent enantioselectivities were realized when R^1 were aliphatic groups (entries 13−14). Then, different ester groups (R^2) were examined under the standard reaction conditions (entries 15−18), and excellent yields and enantioselectivities were achieved regardless of the steric and electronic effects. The absolute configuration of the product **3e** was confirmed by X-ray crystal diffraction.[12]

As shown in Table 3, HDA reactions of *β,γ*-unsaturated *α*-ketoesters with Danishesky's diene provided an efficient approach to various dihydropyrones bearing alkenyl groups with good yield and excellent enantioseletivity. It would be more valuable if the alkenyl group could be replaced by an alkynyl group.[13] With this goal in mind, isopropyl 2-oxo-4-phenylbut-3-ynoate **4a** was selected as a model substrate to examine the substrate scope of the HDA reaction. It was found that a minor modification of the standard reaction conditions led to the formation of products **5a** with excellent yield and enantioselectivity, in which ligand **L2c** was replaced with **L2a** (see Supporting Information (SI) for details).

As presented in Table 4, the scope of 2-oxo-3-ynoates was investigated. Common electron-donating groups in the para position of the phenyl group (R^3) could give a good yield and excellent *ee* value (entries 2−5). However, the reaction yield decreased but the enantioselectivity remained when the *p*-

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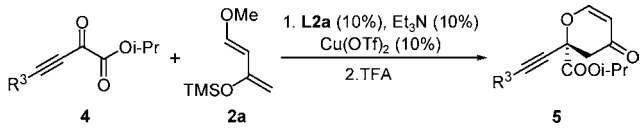
Table 4. Scope of 2-Oxo 3-Ynoate[a]



4 2a 5

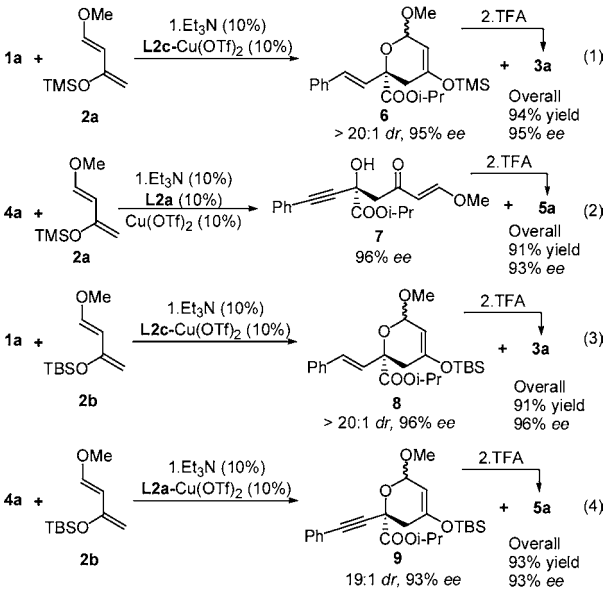
entry	R^3	time (h)	5	yield[b] (%)	ee[c] (%)
1[d]	C_6H_5	24	**5a**	91	93
2	*p*-EtC_6H_4	25	**5b**	89	92
3	*p*-FC_6H_4	25	**5c**	88	92
4	*p*-ClC_6H_4	24	**5d**	81	92
5	*p*-MeC_6H_4	20	**5e**	94	93
6	*p*-OMeC_6H_4	20	**5f**	83	94
7	*p*-$NO_2C_6H_4$	17	**5g**	99	87
8	*m*-MeC_6H_4	20	**5h**	86	92
9[d]	*m*-ClC_6H_4	24	**5i**	82	90
10[d]	TMS	21	**5j**	84	86

[a]Unless otherwise noted, all reactions were performed with **4** (0.2 mmol), **2a** (0.4 mmol), **L2a** (10 mol %), Et_3N (10 mol %), and $Cu(OTf)_2$ (10 mol %) in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]MTBE as the solvent.

methoxyl group was employed (entry 6). When an electron-withdrawing group (*p*-nitro group) was employed, an excellent yield and 87% *ee* were achieved (entry 7). The *meta*-substitution had a little influence on the reaction yields but minimally on the enantioselectivities (entries 8, 9). When an aliphatic group was employed, a moderate yield and enantioselectivity were obtained (entry 10).

Subsequently, the reaction mechanism was investigated. The mechanism of the HDA reaction of Danishefsky's diene with aldehydes has been reported,[4,5a,14] in which two reaction pathways, the concerted (Diels–Alder cycloaddition) and stepwise (Mukaiyama–aldol condensation) pathway, were involved.

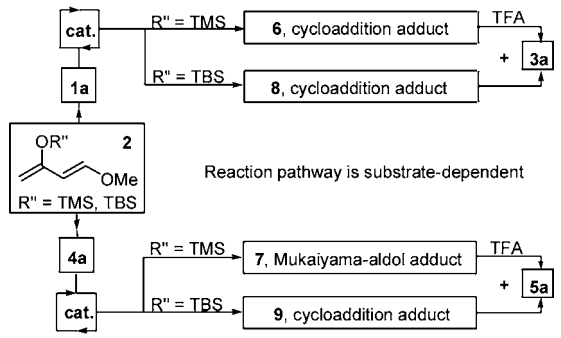
To get a better understanding of the current reaction pathway, some control experiments were carried out. First, for the HDA reaction of Danishefsky's diene with **1a**, analysis of ^1H NMR of the crude mixture showed the HDA reaction should proceed via the cycloaddition adduct **6** [eq 1; see SI for details].



Then, treatment of **6** with TFA gave the product **3a**. The Mukaiyama–aldol adduct was not observed in the crude mixture. This indicated that the HDA reaction of **1a** with **2a** proceeded via a concerted pathway. In contrast, a Mukaiyama–aldol pathway was observed when **4a** was employed as the dienophile and the reaction intermediate **7** was isolated with 96% *ee* [eq 2]. Then, treatment of **7** with TFA gave the product **5a** with 93% *ee*. Nevertheless, the [4 + 2] cycloaddition adduct was not observed in the reaction of **4a** with **2a**. This demonstrated that a stepwise pathway was involved in the HDA reaction of **4a** with **2a**.

Moreover, when the TMS group of Danishefsky's diene was alternated to the TBS group, the HDA reaction of the diene **2b** with **1a** yielded cycloaddition adduct **8** and the product **3a**. Then, treatment of **8** with TFA gave **3a** with 96% *ee* [91% yield, two steps, eq 3]. Similarly, the HDA reaction of **4a** with **2b** afforded intermediate **9** with 19:1 *dr* and 93% *ee*. Then, treatment of **9** with TFA gave the final product **5a** in overall 93% yield and 93% *ee* [eq 4]. This indicated that the HDA reactions of diene **2b** with ketoesters **1a** and **4a** could proceed smoothly to afford corresponding products via a cycloaddition pathway. Intermediates **7**, **8**, **9** were isolated by silica gel chromatography and confirmed by ^1H NMR, ^{13}C NMR, and HRMS. Based on the above-mentioned experiments, the reaction pathway (cycloaddition or Mukaiyama–aldol condensation) was substrate-dependent under the reaction conditions. The reaction pathway not only depended on the dienes but also relied on the ketoesters, as shown in Scheme 2.

Scheme 2. Substrate-Dependent Reaction Pathway



In conclusion, we report the first Cu-catalyzed asymmetric HDA reaction of β,γ-unsaturated α-ketoesters with Danishefsky's diene under mild reaction conditions. A series of chiral dihydropyranones bearing a quaternary center were obtained with excellent enantioselectivities and good to excellent yields. Furthermore, based on the analysis of the isolated intermediates, the reaction pathway was substrate-dependent.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^1H NMR, ^{13}C NMR of new compounds; HPLC profiles and crystallographic data of compound **3e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(12) Details of the crystal structure analysis are provided as SI. CCDC-997035 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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